National Toxicology Program
Toxicity Report Series
Number 51

NTP Technical Report
on the Toxicity Studies of

Methyl Ethyl Ketoxime

(CAS No. 96-29-7)

Administered in Drinking Water
to F344/N Rats and B6C3F$_1$ Mice

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FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program was transferred from NCI to NIEHS. The NTP coordinates the relevant programs, staff, and resources from these public health service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Toxicity Study Report were performed under the direction of NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and most met or exceeded all applicable federal, state, and local health and safety regulations. Animal care and use were in accord and compliance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Toxicity Study Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans requires wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's toxic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Other information about NTP studies is available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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PEER REVIEW

The draft report on the toxicity studies of methyl ethyl ketoxime was evaluated by the reviewers listed below. These reviewers serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of these NTP studies are appropriate and ensure that the Toxicity Study Report presents the experimental results and conclusions fully and clearly.

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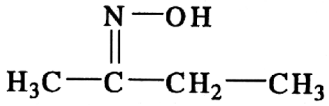
CONTENTS

ABSTRACT



METHYL ETHYL KETOXIME

CAS No. 96-29-7

Chemical Formula: $C_4 H_9 NO$ Molecular Weight: 87.12

Synonyms: 2-Butanone oxime; ethyl methyl ketone oxime; ethyl methyl ketoxime; ethyl-methylketonoxim; MEK-oxime

Trade names: Skino #2; Troykyd anti-skin B; USAF AM-3; USAF EK-906

Methyl ethyl ketoxime is used primarily as an antiskinning agent in alkyd coating resins. Methyl ethyl ketoxime was selected for study because of the potential for human exposure and because of interest in oximes as a chemical class. Toxicity studies of methyl ethyl ketoxime (greater than 99% pure) were carried out in male and female F344/N rats and B6C3F$_1$ mice. The compound was administered in drinking water for 14 days or 13 weeks. In addition, the genetic toxicity of methyl ethyl ketoxime was evaluated by determining mutagenicity in *Salmonella typhimurium* and induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells in vitro, with and without S9 activation. The frequency of micronucleated normochromatic erythrocytes in the peripheral blood of mice from the 13-week study was also determined.

In the 14-day studies, groups of five male and five female rats and mice were given drinking water containing 0, 106, 312, 625, 1,250, or 2,500 ppm methyl ethyl ketoxime. The mean body weight gain of male rats in the 2,500 ppm group was significantly less than that of the controls; the final mean body weight of male mice in the 2,500 ppm group was also less than that of the controls. Spleen weights were increased in male and female rats in the 1,250 and 2,500 ppm groups. No chemical-related gross lesions were observed. Microscopic tissue evaluations were not performed.

In the 13-week studies, groups of 10 male and 10 female rats were given drinking water containing 0, 312, 625, 1,250, 2,500, or 5,000 ppm and groups of 10 male and 10 female mice were given drinking water containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm. Mean body weights and body weight gains of 2,500 and 5,000 ppm male rats and 10,000 ppm male and female mice were less than those of the controls; mean body

weight gains of male rats in the 1,250, 2,500 and 5,000 ppm groups and females in the 2,500 and 5,000 ppm groups were also less than those of the controls. Hematology results of this drinking water study indicate that methyl ethyl ketoxime induces a methemoglobinemia and a responsive Heinz body anemia. Liver and spleen weights were generally significantly greater than those of the controls in male and female rats exposed to 1,250 ppm or greater; spleen weights were also increased in male and female mice in the 10,000 ppm groups. Kidney weights were significantly greater in male rats in the 5,000 ppm group and in female rats exposed to 1,250 ppm or greater than those of the controls. Microscopically, there were exposure-related increases in the incidences and severities of hematopoietic cell proliferation in the spleen at exposure concentrations of 625 ppm or greater in male and female rats and at 5,000 and 10,000 ppm in male and female mice. A significant increase in the incidence of hematopoietic proliferation in the bone marrow was observed in rats exposed to 625 ppm or greater. Liver Kupffer cell erythrophagocytosis and hemosiderin pigmentation, as well as renal tubule hemosiderin pigmentation, occurred in exposed rats and mice. Other lesions observed include hyperplasia of the transitional epithelial lining of the urinary bladder in male and female mice exposed to 2,500 ppm or greater and degeneration of the nasal olfactory epithelium in male and female rats in the 2,500 and 5,000 ppm groups, male mice in the 5,000 and 10,000 ppm groups, and female mice exposed to 2,500 ppm or greater.

Methyl ethyl ketoxime is extensively metabolized and does not accumulate in tissues. Single gavage doses of 2.7, 27, or 270 mg/kg administered to rats were primarily converted to carbon dioxide, mostly in the first 24 hours after dosing. After intravenous administration, less radioactivity on a percentage basis was excreted as carbon dioxide than in the gavage study, and more of the administered dose was excreted in urine and as volatiles. Following dermal administration, significantly greater amounts of volatiles were excreted than after gavage or intravenous administration. The 270 mg/kg gavage dose may result in saturation of a metabolic pathway(s). There is some evidence that the ketoxime is metabolized to the ketone and, presumably, hydroxylamine.

Methyl ethyl ketoxime was mutagenic in *Salmonella typhimurium* strain TA1535 when tested in the presence of hamster liver S9 activation enzymes; results of mutagenicity testing were negative in strains TA97, TA98, and TA100, with and without exogenous metabolic activation. No induction of sister chromatid exchanges or chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with methyl ethyl ketoxime, with or without S9, and no increase in the frequency of micronucleated erythrocytes was noted in peripheral blood obtained from male and female mice administered methyl ethyl ketoxime in drinking water for 13 weeks.

In summary, the major target of methyl ethyl ketoxime is the erythrocyte; the no-effect level for erythrotoxicity is 625 ppm in male rats and 312 ppm in female rats based on erythrocyte counts after 13 weeks of exposure. The no-effect level for hematopoietic toxicity is 312 ppm in rats based on erythroid cell hyperplasia in bone marrow and 2,500 ppm in mice based on hematopoietic cell proliferation in the spleen. Hematology results of this drinking water study indicate that methyl ethyl ketoxime induces a methemoglobinemia and a responsive Heinz body anemia. Methyl ethyl ketoxime was at most weakly genotoxic; it induced mutations in *S. typhimurium* under very specific conditions, but it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells *in vitro* or increase the frequency of micronucleated erythrocytes in mice treated *in vivo*.